REMARKS

I. Status of the Claims

Claims 1-4 and 6-19 have been examined. Claims 2-6 and 18 have been canceled. Claims 1, 7-14 and 19 have been amended. Claims 20-29 have been added. Claims 1, 7-17 and 19-29 are now pending in the application.

II. Rejections under 35 U.S.C. § 102

el Kouni

Claims 1-4 and 17-19 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,670,331 ("*el Kouni*"). *Office Action* at p. 2. Applicants respectfully traverse this rejection.

In the "Background" section, *el Kouni* describes prior art uses of 5-fluorouracil as a drug for the treatment of certain cancers. *el Kouni* at col. 1, lines 14-20. The Examiner contends that: (1) 5-fluorouracil "would inherently be labeled" with a non-radioactive label, such as C-13, N-15, and O-18, since these isotopes have some natural abundance in 5-fluorouracil; and (2) the "intended use of the claimed invention" does not convey a structural difference from the prior art and thus, the limitation is not granted patentable weight. *Office Action* at p. 2.

Applicants respectfully disagree because one of ordinary skill in the art would readily appreciate that the term "labeled with a non-radioactive isotope" in currently presented claims 1, 12, and 19 refers to the non-radioactive isotope being present in an amount greater than the amount naturally present. Nonetheless, to expedite prosecution, claim 1 has been amended to recite certain pyrimidine compounds

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previously recited in claim 4. Claim 1 has also been amended to incorporate the limitations of claim 6, wherein at least one of C, O and N is labeled with a non-radioactive isotope selected from ^{13}C, ^{18}O and ^{15}N, respectively. As a result, claims 2-6 have been canceled.

The list of pyrimidine compounds recited in claim 1 does not include 5-fluorouracil disclosed in *el Kouni*. Moreover, *el Kouni* does not disclose, teach, or suggest any of the pyrimidine compounds recited in amended claim 1.

Accordingly, Applicants respectfully request withdrawal of this rejection.

Fujii

Claims 1-4 and 17-19 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,328,229 ("*Fujii*"). *Office Action* at p. 3. Applicants respectfully traverse this rejection.

Fujii is directed to anti-cancer compositions comprising 5-fluorouracil. *See, e.g.*, *Fujii* at col. 1, lines 8-10. As discussed above, claim 1 has been amended to recite specific pyrimidine compounds. The list of pyrimidine compounds recited in claim 1 does not include 5-fluorouracil. Moreover, *Fujii* does not disclose, teach, or suggest any of the recited pyrimidine compounds.

Accordingly, Applicants respectfully request withdrawal of this rejection.

Triplett

Claims 1-4 and 17-19 stand rejected under 35 U.S.C. § 102(b) as being anticipated by J. Labelled Compounds and Radiopharmaceuticals, Vol. XIV, pp. 35-41, 1989 ("*Triplett*"). *Office Action* at p. 3. Applicants respectfully traverse this rejection.

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Triplett describes the preparation of various ^{13}C-labeled compounds, including uracil. *See Abstract.* As discussed above, claim 1 has been amended to recite specific pyrimidine compounds. The list of pyrimidine compounds recited in claim 1 does not include uracil. Moreover, *Triplett* does not disclose, teach, or suggest any of the recited pyrimidine compounds.

Accordingly, Applicants respectfully request withdrawal of this rejection.

III. Rejections under 35 U.S.C. § 103

el Kouni or *Creasey* in view of *Katzman*

Claims 1-4 and 6-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either one of *el Kouni* or Clinical Pharmacology and Therapeutics ("*Creasey*") in view of U.S. Patent No. 5,944,670 ("*Katzman*"). *Office Action* at pp. 3-4. *el Kouni* is cited by the Examiner as describing "methods of determining pyrimidine metabolism comprising administering radiolabeled forms thereof" and "determining the safe dose of the drug." *Id.* The Examiner cites *Creasey* for describing a method of "determining pyrimidine metabolism comprising administering a C-14 labeled 5-fluorouracil for determination of dosage." *Id.* at p. 4. The Examiner admits that *el Kouni* and *Creasey* do not specifically disclose the use of C-13, N-15, or O-18. *Id.* Thus, *Katzman* is cited as teaching the interchangeability of C-13 and C-14 labels and their use in breath tests that administer labeled compounds. *Id.* Applicants respectfully traverse this rejection.

el Kouni is discussed above. *Creasey* describes intravenous administration of uracil-2-^{14}C to patients with far-advanced neoplastic disease. *Creasey* at p. 274.

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Respiratory $^{14}CO_2$ was passed through a saturated barium hydroxide solution and the resulting barium carbonate was subjected to a scintillometer. *Id.*

Katzman describes a breath test for detecting the presence of Chlamydia in a subject by administering a substrate to the subject and then detecting the cleavage product in the exhaled breath. *Katzman* at col. 3, lines 27-33. While *Katzman* provides general desired features of the substrate, the only substrate specifically named is L-leucine p-nitro anilide. *Id.* at col. 5, lines 65-66.

Applicants respectfully disagree that the combined teachings of the cited references render amended claim 1 unpatentable. As discussed above, claim 1 has been amended to recite specific pyrimidine compounds. *el Kouni*, *Creasey*, or *Katzman*, either alone or in combination, do not teach or suggest any of the labeled compounds recited in claim 1.

Applicants also respectfully submit that the cited references do not render independent claim 7 unpatentable. Nonetheless, to expedite prosecution, claim 7 has been amended to require performing administering steps (i), (ii), and (iii), *i.e.*, administering to a subject (i) uracil or thymine, (ii) dihydrouracil or dihydrothymine, and (iii) β-ureidopropionic acid or β-ureidoisobutyric acid, wherein at least one of C, O, and N in (i), (ii), and (iii) is labeled with a non-radioactive metabolite. Steps (i), (ii), and (iii) also recite measuring a non-radioactive isotope-labeled metabolite. Support for these claim amendments can be found in the specification at least at p. 21, line 13 to p. 22, line 13.

The cited references, either alone or in combination, fail to teach or suggest performing all three steps (i), (ii), and (iii), as recited in amended claim 7. At best, each

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reference teaches administering only one compound. The combined teachings of the references fail to suggest multiple administering steps and do not describe the specific combination of compounds in steps (i) to (iii) of amended claim 7.

Claim 14 has been amended to recite a method for determining a dosage regimen comprising administering a preparation wherein at least one of C and O is labeled with a non-radioactive isotope ^{13}C and ^{18}O, respectively, and measuring a non-radioactive isotope-labeled CO_2 excreted in the expired air. *el Kouni* and *Creasey* do not teach or suggest a method for determining a dosage regimen comprising administering a preparation wherein at least one of C and O is labeled with a non-radioactive isotope ^{13}C and ^{18}O. At best, *el Kouni* and *Creasey* teach the use of ^{14}C-labeled compounds. *Katzman* only describes a breath test and not teach or suggest a method for determining a dosage regimen. Accordingly, the cited references, either alone or in combination, fail to teach or suggest each of the limitations of amended claim 14.

New independent claim 21 recites steps (i) and (ii), *i.e.*, administering to a subject (i) dihydrouracil or dihydrothymine, and (ii) β-ureidopropionic acid or β-ureidoisobutyric acid, wherein at least one of C, O, and N in (i) and (ii) is labeled with a non-radioactive metabolite. Steps (i) and (ii) also recite measuring a non-radioactive isotope-labeled metabolite. As discussed above, each of the references only teaches the use of one administering step. Moreover, none of the references teaches or suggests administering any of the compounds listed in claim 21.

Accordingly, Applicants respectfully request withdrawal of this rejection.

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Abramson

Claims 1-4, 6-8, and 10-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,355,416 ("*Abramson*"). *Office Action* at pp. 4-5. According to the Examiner, *Abramson* discloses the use of compounds such as thymine to monitor "uptake of the thymine in DNA in the body." *Id.* The Examiner also alleges that *Abramson* discloses "[o]ral administration of such tracers ... in example 1." *Id.* Applicants respectfully traverse this rejection.

Applicants respectfully disagree that *Abramson* broadly teaches "oral administration" of all compounds, as alleged. Example 1 of *Abramson* teaches oral administration only of ^{15}N, ^{13}C-labeled caffeine. *Abramson* also teaches administering to a "sample." *See*, e.g., independent claims 1-3, 8, 10, and 18. Thus, there is no suggestion in *Abramson* to directly administer a pyrimidine compound or its metabolite to a subject, much less the pyrimidine compounds recited in amended claim 1. Moreover, *Abramson* does not teach or suggest the multiple administering steps of claims 7 and 21, nor does *Abramson* teach or suggest a method of determining a dosage regimen, as recited in claim 14.

Accordingly, Applicants respectfully request withdrawal of this rejection.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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